DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office

60 8th Street, N.E.
Atlanta, Georgia 30309

g16421

August 14, 2001

VIA FEDERAL EXPRESS

Dr. Jeffrey S. Kiel
President
Kiel Laboratories, Inc.
2225 Centennial Drive
Gainesville, Georgia 30504

**WARNING LETTER**
**(01-ATL-73)**

Dear Dr. Kiel:

An inspection of your drug manufacturing facility was conducted between July 2 and July 26, 2001, by Investigator Penny H. McCarver of this office. Our investigator documented several significant deviations from the Current Good Manufacturing Practice Regulations (GMPs) as set forth in Title 21 of the Code of Federal Regulations (21 CFR), Part 211. These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act).

You have failed to adequately validate the manufacturing processes for all of your drug products. These products include [redacted] and [redacted] You could not provide documented evidence which established a high degree of assurance that the manufacturing processes in use could consistently produce products meeting their predetermined specifications and quality attributes, both initially and throughout their labeled expiration date.

You failed to appropriately respond to significant indicators of potential product quality issues in your validation lots of [redacted] tablets. Multiple assay stability failures and borderline passing results were noted in all three validation lots. Lot GA527, the only lot placed on accelerated stability study, was noted to fail at the two and three month test station. Your firm decided to release these validation lots despite these failing results and after initiating an investigation into the effect of adding desiccant to bottles of this product. The decision to release these lots was reportedly based on acceptable stability data of your biobatch lot GA194.

However, the manufacturing process utilized for your biobatch lot differed from that used in the three validation lots produced. No comparison was made in your process validation assessment of the current commercial manufacturing process and the process used in the original biobatch. The biobatch production utilized a drying room warmed with portable heaters at a drying temperature of [redacted] and no moisture specification was established. During manufacture of the biobatch the blended granulation was screened and reblended for an additional [redacted] minutes, which is not done in the commercial batches. The biobatch was also blended for [redacted] minutes and the current process specifies a [redacted] minute blend. It is not known what effect, if any, the differences would have on the composition, dissolution, and bioequivalence of these tablets.

In addition, you could not provide justification for the current granulation drying temperature range of [redacted] C. You have also not established a specification for the granulation drying step or for the mixer speed setting utilized in the dry blending step.

You have failed to appropriately validate the manufacturing process for your [redacted] You have failed to establish mixing times and speeds for all critical mixing processes. Your Addendum to [redacted] Validation Reports, approved during the inspection, states "it is impossible to establish mixing specification ranges based on the development batches." You apparently plan to develop the final specifications based on data generated during the production of future batches. Your final mixing time specified in the batch production record is [redacted] minutes, although the sampling times utilized during the process validation ranged from [redacted] minutes. There was no data to justify the conversion steps for [redacted] and [redacted] There was also no time specified for these conversion steps.

The first batch (Lot GA823) produced after the completion of the three validation batches was rejected due to high and low out-of-specification (OOS) assay results for all three active ingredients. These failures were attributed to inappropriate addition rate and a lower mixing rate used to dilute some of the solutions. Neither the Master Batch Record nor the Process Validation Report addressed these critical rates in the process.

You have failed to appropriately validate the commercial manufacturing process for [redacted] You have failed to establish mixing times and speeds for all critical mixing processes. You established a final mixing time of [redacted] minutes, but the sampling times used during the process validation were [redacted] minutes.

The process validation samples were assayed using an HPLC method that had not been validated. The method validation used for both products ([redacted] and [redacted] did not include a protocol that included specifications and acceptance criteria. The validation failed to include any determination as to the accuracy of the method. The method validation was not reviewed and approved until during the

current inspection. Lots of both products were released for distribution prior to completion of the method validation.

Several other instances were noted where you failed to conduct a complete review of all production and control records by quality control to determine compliance with all established written procedures prior to release for distribution. Your firm released [redacted] Lots GA831, GA832, and GA833 prior to review and approval of the completed Process Validation Report and the HPLC assay method validation. Your firm released two lots of [redacted] (GA821 and GA822) and three lots of [redacted] (GA831, GA832, and GA833) prior to review and approval by Quality Assurance as per your SOP E008A entitled Procedure for Releasing Product for Shipment. Your firm released two validation batches of [redacted] and three lots of [redacted] prior to completion of the USP Preservative Efficacy testing.

Your firm failed to appropriately respond to OOS results by conducting manufacturing investigations or the implementation of corrective action as necessary. Your SOP B008E, Laboratory Retest and Failing Results Policy, requires further investigation if the lab investigation and retesting indicates a confirmed OOS result. The procedure further requires a written report with sufficient detail to show why failing results occurred and the corrective action taken. Your firm failed to complete written reports for any manufacturing investigations conducted in accordance with these procedures. Examples of this include Lot GA742 of [redacted] Tablets which had content uniformity failures noted during in-process testing, OOS assay result for Lot GA761 of [redacted] Tablets, Lot GA734 of [redacted] Tablets which revealed OOS assay results in blend uniformity samples, and Lot GA830 of [redacted] which revealed OOS assay results for [redacted]. These OOS results were not investigated to determine the cause of the failures, extent of the problem, and potential impact upon other lots.

You have failed to appropriately investigate and respond to OOS results obtained during analytical testing. Testing of Lot GA814 of [redacted] Capsules revealed an OOS assay value in a blend uniformity sample. Your firm failed to follow your SOP for handling OOS results. There was no assignable cause for the results but the sample was retested only twice. Adequate justification was not provided for your discounting of the OOS result. No corrective action was taken even though a possible sample preparation error was noted as a potential cause.

Low OOS assay results for [redacted] and [redacted] were noted in mixing samples during processs validation of [redacted] Lot GA832. A clearly assignable cause for the OOS result was not found. Your firm prepared samples again and retested the lot. Only the passing retest results were reported.

OOS assay results were noted in Lot GA715 of [redacted] tablets. No assignable cause was determined and you failed to follow your retest procedure. You merely reinjected the original sample and one additional sample preparation. These

test results were averaged to obtain a passing result. A blend uniformity OOS assay result was obtained in Lot GA745 of [redacted] tablets. The original sample was reinjected and an additional sample prepared was also tested. The average of all tests was reported as an acceptable result.

You have failed to validate the HVAC system used to control temperature and relative humidity in your manufacturing and warehouse areas. No formal specifications for temperature or humidity have been established for these areas. You were noted to have portable chart recorders for monitoring of temperature and humidity in Suites 1 and 2 and one recorder was noted in the warehouse. A wide range of temperatures and humidity was noted in our review of the data from the monitored areas. The results exceeded your proposed specifications shown to Investigator McCarver in your draft SOP E073. These proposed ranges would appear to be excessive particularly since you currently manufacture at least one product that has exhibited sensitivity to humidity.

The violations cited in this letter are not intended to be a statement of all the violations that may exist for products marketed by your firm. It is your responsibility to assure that all your products are in compliance with federal laws and regulations. The above deviations were included on the Inspectional Observations (FDA 483) which was issued to and discussed with you at the conclusion of the inspection. The specific violations noted in this letter and in the FDA 483 are symptomatic of underlying problems in your firm's quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

Of particular concern is the fact that many of the above violations were pointed out to you previously. These deficiencies are similar or, in some cases, identical to deficiencies observed during previous inspections at your firm in November 1997 and May 1999. This demonstrates a continuing pattern of non-compliance with GMPs. We refer you to the Inspectional Observations left with you at the close of those inspections, as well as this one. Copies of these previous FDA 483's are enclosed for your review. Although improvements had been noted during the previous inspection, you have not remained diligent in keeping your firm in compliance.

Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering contract awards. Additionally, pending New Drug Applications, Abbreviated New Drug Applications, or export approval requests may not be approved until the above violations are corrected. Failure to promptly correct these violations may result in regulatory action without further notice. Such actions include seizure and/or injunction.

Within fifteen (15) working days of your receipt of this letter, please notify this office in writing of the specific steps you will take to correct the noted violations. If corrective actions cannot be completed within 15 working days, state the reason for the delay and

the time frame within which corrections will be completed. Due to these ongoing problems, we would welcome an opportunity to discuss your firm's status at the district office. Your reply to this letter should be sent to the Food and Drug Administration at the above letterhead address to the attention of Philip S. Campbell, Compliance Officer. You can also contact Mr. Campbell at (404) 253-1280 to set up the meeting discussed above.

Sincerely,

Barbara G. Woodfor

Ballard H. Graham, Director
Atlanta District

Enclosures